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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/933,131	08/21/2001	Li Zhang	10723-26	4949

7590 02/11/2003

MICHELINE & GRAVELLE
Bereskin & Parr
Box 401
40 King Street West
Toronto, ON M5H 3Y2
CANADA

EXAMINER
BELYAVSKYI, MICHAIL A

ART UNIT	PAPER NUMBER
1644	8

DATE MAILED: 02/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/933,131	ZHANG ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *2,3 and 8-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 August 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election of Group I, claims 1 and 4-7 in Paper No. 7 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 2-3 and 8-11 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

Claims 1 and 4-7 are under consideration in the instant application.

2. Formal drawings have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in ABANDONMENT of the application.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 4-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method to inhibit lymphoma cell growth and a method to treat lymphoma, comprising administering an effective amount of a regulatory T cell having the phenotype $CD3^+$ αβ $-TcR^+$ $CD4^-CD8^-CD44^-$ Cd28-$NK1.1^-$ does not reasonably provide **enablement** for a method to inhibit any tumor cell growth and a method to treat or prevent any cancer comprising administering an effective amount of a regulatory T cell having the phenotype $CD3^+$ αβ $-TcR^+$ $CD4^-CD8^-CD44^-$ Cd28-$NK1.1^-$. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the limited working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification only discloses that administering effective amount of regulatory T-cell having the phenotype $CD3^+$ αβ $-TcR^+$ $CD4^-CD8^-CD44^-$ Cd28-$NK1.1^-$ can inhibit growth of lymphoma cells in Scid (severe combined immunodeficient) mouse as a test animal (Example 1 of the Specification as filed).

The specification does not adequately teach how to effectively inhibit any tumor cell growth or proliferation such as treating or preventing any cancer or reach any therapeutic endpoint in mammals by administrating effective amount of regulatory T-cell having the phenotype $CD3^+$ αβ $-TcR^+$ $CD4^-CD8^-CD44^-$ Cd28-$NK1.1^-$. It is not clear that reliance on the *in vivo* data of treating lymphomas , that was induced in immunodeficient mice in response to A20 B cell leukemia/lymphoma cells inoculation into said mice, after administrating effective amount of regulatory T-cell having the phenotype $CD3^+$ αβ $-TcR^+$ $CD4^-CD8^-CD44^-$ Cd28-NK1.1 accurately reflects the relative mammal efficacy of the claimed therapeutic strategy. The specification does not teach how to extrapolate data obtained from limited *in vivo* assay studies to the development of effective *in vivo* mammalian therapeutic treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy a method to inhibit any tumor cell growth and treating or preventing any cancer comprising administering an effective amount of a regulatory T cell having the phenotype $CD3^+$ αβ $-TcR^+$ $CD4^-CD8^-CD44^-$ Cd28-$NK1.1^-$.

Further, the burden of enabling the prevention of any cancer (i.e. the need for additional testing) would be greater than that of enabling a treatment due to the need to screen those humans susceptible to such diseases and the difficulty of proof that the administration of $CD3^+$ αβ $-TcR^+$ $CD4^-CD8^-CD44^-$ Cd28-$NK1.1^-$ cells was the agent that acted to prevent the condition. Moreover, *preventing* would require administration of the claimed $CD3^+$ αβ $-TcR^+$ $CD4^-CD8^-CD44^-$ Cd28-$NK1.1^-$ cells prior to the development of the tumor. However, there is no guidance in the specification for determining the appropriate time prior to the development of tumors to begin the therapy . Further, the specification does not provide guidance as to how one skilled in the art would go about screening those patients susceptible to any cancer within the scope of the presently claimed invention. Nor is guidance provided as to a specific protocol to be utilized in order to prove the efficacy of the presently claimed a method to inhibit any tumor cell growth and treating or preventing any cancer comprising administering an effective amount of a regulatory T cell having the phenotype $CD3^+$ αβ $-TcR^+$ $CD4^-CD8^-CD44^-$ Cd28-NK1.1. The exemplification is drawn to a preventive mode in a mouse model where a define tumor burden was used in a challenge studies to demonstrate anti-tumor activity of administering an effective amount of a regulatory T cell having the phenotype $CD3^+$ αβ $-TcR^+$ $CD4^-CD8^-CD44^-$ Cd28-$NK1.1^-$.

Moreover, an effective preventive protocol for the prevention of a tumor in a human patient is a subject to a number of factors which enter the picture beyond simply the administration of an effective amount of a regulatory T cell having the phenotype $CD3^+$ αβ $-TcR^+$ $CD4^-CD8^-CD44^-$ Cd28-NK1.1. Demonstration that administering effective amount of regulatory T-cell having the phenotype $CD3^+$ αβ $-TcR^+$ $CD4^-CD8^-CD44^-$ Cd28-$NK1.1^-$ can prevent growth of lymphoma cells in Scid mouse, that was induced in said mouse in response to A20 B cell leukemia/lymphoma cells inoculation cannot alone support the predictability of the method of preventing any tumor growth. The establishment and growth of a tumor is a subject to variables. The ability of a host to suppress and thereby prevent the tumor from establishing itself will vary depending upon factors such as the condition of the host, the type of tumor (rapidly proliferating or slowly proliferatinf) and the tumor burden.

Chatterjee et al. (Cancer Immunol. Imunother., 1994, v.38, pages 75-82 see Introduction) state the art recognized experience that for any novel therapy, the transition for the laboratory to the clinic (animal experiments to the bedside) is a quantum leap. Results obtained under controlled conditions and in inbred animals, as in the instant specification where Scid (severe combined immunodeficient) mice are used as a test animal, often differ from the clinical response obtained in patients. This applies to strategies drawn to cancer therapy. For example, Dermer (Biotechnology 12: 320, 1994) states that the widely disparate character of human tumor cells contributes greatly to chemotherapy's continued ineffectiveness against cancer. Tumor burden and antigenic drift continue to present serious burdens for successful cancer therapy in vivo. Tumors are classified as immunogenic or non-immunogenic, solid or hematological in nature. Effective cancer strategies should be designed to deal effectively with the nature of each of these classifications.

In addition, Sussman et al.(Annals of Surgical Incology, 1994, v.1 p296-306) teach that hampering the development of the effective immunotherapy of human cancer is the poorly defined immunosuppression that occurs in cancer patient, due to the presence of tumor suppressor cells in tumor-bearing host that abrogate the antitumor reactivity of adoptively transferred immune lymphocytes. Sussman et al further teach that there is significantly less information regarding the phenomenon of tumor-induced suppression that may inhibit the development of immune cells. (see entire document, page 303 in particular).

Simillary, Klingemann (J. of Hematotheraphy and Stem Cell Research, 2001, v.10, p 23 –26) teaches that cellular adoptive immunotherapy should never bee expected to be useful and effective against all tumor burden. Such therapy should be viewed as a part of a comprehensive cancer treatment approach that may include chemotherapy, radiation and other novel treatment. Expecting anything more would be unrealistic and may call a negative outcome of studies if they are designed with such an end point in mind (see entire document, page 25 in particular).

The specification does not provide sufficient teaching as to how it can be assessed that treatment or prevention of any tumors or any cancer was achieved after administering an effective amount of a regulatory T cell having the phenotype $CD3^+$ $\alpha\beta$ $-TcR^+$ $CD4^-CD8^-CD44^-$ Cd28-$NK1.1^-$.

The specification provides insufficient guidance with the issue raised above and no evidence has been provided which would allow one skill in he art to predict the efficacy of the claimed method with a reasonable expectation of success.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method to inhibit any tumor cell growth or proliferation and method to treat or prevent any cancer comprising administering an effective amount of a regulatory T cell having the phenotype $CD3^+$ $\alpha\beta$ $-TcR^+$ $CD4^-CD8^-CD44^-$ Cd28-$NK1.1^-$. in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

4. No claim is allowed.

5. The prior art does not teach or suggest the claimed invention recited in claims 1 and 4-7.

6. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is (703) 308-4232. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Michail Belyavskyi, Ph.D.
Patent Examiner
Technology Center 1600
February 10, 2003

Christina Chan

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600